Evaluation of hepatitis C treatment-as-prevention within an Australian prison prospective cohort: The SToP-C study

Authors and affiliations:

Behzad Hajarizadeh (PhD),[1] Prof Jason Grebely (PhD),[1] Marianne Byrne (MPH),[1] Pip Marks (MPH),[1] Prof Janaki Amin (PhD),[1,2] Hamish McManus (PhD),[1] Prof Tony Butler (PhD),[1] Evan B Cunningham (PhD),[1] Prof Peter Vickerman (PhD),[3] Natasha K Martin (PhD),[3,4] John G McHutchison (MD),[5] Diana M Brainard (MD),[6] Prof Carla Treloar (PhD),[7] Prof Georgina M Chambers (PhD),[8] Luke Grant (MSc),[9] Colette Mcgrath (MSc),[10] Prof Andrew R Lloyd (PhD),*[1] Prof Gregory J Dore (PhD),*[1] on behalf of the SToP-C study group

*Contributed equally

1. The Kirby Institute, UNSW Sydney, Sydney, Australia;

2. Faculty of Medicine and Health Sciences, Macquarie University, Sydney, Australia;

3. Population Health Sciences, University of Bristol, Bristol, UK;

4. Division of Infectious Diseases & Global Public Health, University of California San Diego, San Diego, USA;

5. Assembly Biosciences, San Francisco, USA;

6. Gilead Sciences Inc., Foster City, USA;

7. Centre for Social Research in Health, UNSW Sydney, Sydney, Australia;

8. Centre for Big Data Research in Health, UNSW Sydney, Sydney, Australia;

9. Corrective Services NSW, Sydney, Australia;

10. Justice Health and Forensic Mental Health Network, NSW Health, Sydney, Australia

Corresponding Author:

Professor Gregory Dore

The Kirby Institute, Wallace Wurth Building, UNSW Sydney, NSW 2052 Australia

E-mail: gdore@kirby.unsw.edu.au ; Phone: +61 2 9385 0900

ABSTRACT

Background: Limited empirical evidence exists for hepatitis C virus (HCV) treatment-as-prevention. The Surveillance and Treatment of Prisoners with hepatitis C (SToP-C) study assessed HCV treatment-as-prevention in four Australian prisons.

Methods: SToP-C is a non-randomised trial, including a pre/post analysis within a prospective longitudinal cohort of people incarcerated in two maximum- (male) and two medium-security prisons (one male, one female). All prison inmates at least 18 years were eligible for enrolment. Participants were enrolled from late-2014 to 2019. Following HCV testing, participants were monitored for risk behaviors and HCV, among three sub-populations: 1) uninfected (HCV antibody negative); 2) previously infected (HCV antibody positive, HCV RNA negative); 3) infected (HCV antibody and HCV RNA positive). Uninfected and previously infected (at-risk) participants were followed every 3-6 months for HCV primary infection and re-infection, respectively. Infected participants were assessed for treatment, initially standard of care treatment (by prison health services), followed by direct-acting antiviral (DAA) treatment scale-up from mid-2017 (12 weeks sofosbuvir/velpatasvir, through SToP-C). Participants were followed until study closure in November 2019. The primary study outcome was HCV incidence compared between pre- and post-treatment scale-up periods among participants at risk of HCV primary infection or re-infection. The trial was registered with ClinicalTrials.gov (identifier: NCT02064049)

Findings: Of 3,691 participants enrolled, 719 (19%) had detectable HCV RNA and 2,965 were at-risk of primary infection (n=2,240) or re-infection (n=725) at baseline. DAA treatment was initiated in 349/499 eligible participants during the treatment scale-up period. Among at-risk population with longitudinal follow-up (n=1,643; median age 33 years; 82% male), 31% reported injecting drug use in prison. HCV incidence declined by 48%, from 8.31 to 4.35/100 person-years between pre- and post-treatment scale-up periods [Incidence Rate Ratio (IRR):

0.52, 95%CI: 0.36, 0.78]. Incidence of primary infection declined from 6.64 to 2.85/100 person-years (IRR: 0.43, 95%CI: 0.25, 0.74), while incidence of re-infection declined from 12.36 to 7.27/100 person-years (IRR: 0.59, 95%CI: 0.35, 1.00). Among participants reporting injecting drug use in the current imprisonment, incidence of primary infection declined from 39.08 to 14.03/100 person-years (IRR: 0.36, 95%CI: 0.16, 0.80), and incidence of re-infection declined from 15.26 to 9.34/100 person-years (IRR: 0.61, 95%CI: 0.34, 1.09). Adjusted analysis indicated a significant reduction in HCV risk between pre- and post-treatment scale-up periods (adjusted Hazard Ratio: 0.50, 95% CI: 0.33, 0.76).

Interpretation: DAA treatment scale-up was associated with reduced HCV incidence in prison, indicative of HCV treatment-as-prevention. The findings support broad DAA treatment scale-up among incarcerated populations.

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Keywords: HCV; direct-acting antivirals; correctional setting; injecting drug use; clinical trial

RESEARCH IN CONTEXT

Evidence before this study

We searched MEDLINE and Scopus for papers published up to 10 September 2020, using a combination of search terms, including ("hepatitis C" OR HCV) AND treatment* AND (prevent* OR incidence) AND ("direct acting antiviral*" OR DAA) AND (prison* OR jail* OR correction* OR convict*). We found no interventional studies investigating hepatitis C virus (HCV) treatment-as-prevention in prison settings. Some repeated surveys demonstrated decreased HCV prevalence following increased uptake of HCV treatment in prisons. However, these studies did not include systematic surveillance and did not evaluate risk status or HCV incidence. Some modelling studies have suggested that increasing HCV treatment uptake in prisons and improved harm reduction strategies could control HCV transmission and decrease HCV incidence. However, there is limited empirical evidence to support these findings in a real-world setting.

Added value of this study

To our knowledge, this is the first HCV treatment-as-prevention study in the prison setting, and the largest interventional HCV treatment-as-prevention study in any setting. This study provides empirical evidence of HCV treatment-as-prevention, with the HCV incidence almost halved (from 8.3 to 4.4/100 person-years) following rapid scale-up of sofosbuvir/velpatasvir treatment within four prisons, including several thousand participants in two maximum and two medium-security prisons. The magnitude of the HCV treatment-as-prevention effect was larger against primary HCV infection than HCV re-infection, and in participants who reported injecting drugs in their current imprisonment.

Implications of all the available evidence

The World Health Organization has set a goal to eliminate HCV as a major global public health threat by 2030, including reducing the number of new HCV infections by 80%. In most countries, prisons are a priority setting for HCV elimination efforts, given the high prevalence and incidence in most prisons. The findings of the SToP-C study highlight both the feasibility and the positive impact of HCV direct-acting antiviral treatment scale-up in reducing the incidence of HCV infection in the prison setting. This demonstration of effective HCV treatment-as-prevention should encourage enhanced access to direct-acting antiviral treatment, including rapid scale-up of treatment uptake among incarcerated populations.

INTRODUCTION

Globally, an estimated 71 million people have chronic hepatitis C virus (HCV) infection.[1] The advent of direct-acting antiviral (DAA) regimens have led a revolution in HCV therapy,[2] with simple (once daily dosing oral regimens), well-tolerated, short-duration (8-12 weeks), pan-genotypic treatment with cure rates >95%. The broad implementation of DAA therapy has considerable public health potential, with the World Health Organization setting ambitious HCV elimination impact targets, including an 90% reduction in HCV incidence, 80% of the infected population treated, and a 65% reduction in HCV mortality by 2030.[3]

The capacity to achieve HCV elimination targets depends on many factors, but provision of DAA therapy to marginalized populations with HCV infection is crucial. People who inject drugs are incarcerated at high rates for drug-related crimes.[4] Thus, in many countries, people who inject drugs and people who are incarcerated are priority populations, given their high burden of HCV infection, and their role in ongoing HCV transmissions.[5,6] Delivery of effective HCV prevention and treatment interventions to these two populations is central to elimination efforts. Improving HCV prevention measures in the prisons is also important for controlling HCV in the community, given high transitioning between prison and community.

Treatment-as-prevention, initially used in the context of HIV therapy,[7] incorporates treatment as a tool for limiting spread of an infection in epidemics in a particular setting.[8] Although mathematical modelling has demonstrated the potential for HCV treatment-as-prevention among people who inject drugs and in prison settings,[5,6,9] very limited empirical data exists to confirm these modelling-based impact projections in a real-world setting. The demonstration of HIV treatment-as-prevention has been pivotal to the global HIV response and elimination

efforts.[7,10] Similarly, well-conducted, large-scale clinical trials are now required to evaluate HCV treatment-as-prevention.

We hypothesised that rapid DAA-based treatment scale-up in prison would reduce HCV transmission, defined by the incidence of primary HCV infection and HCV re-infection. The Surveillance and Treatment of Prisoners with hepatitis C (SToP-C) evaluated the impact of DAA treatment scale-up on HCV incidence in four Australian prisons.

METHODS

Study setting and design

The SToP-C study was a non-randomised clinical trial evaluating HCV treatment-as prevention, including a pre/post analysis of HCV incidence within a longitudinal cohort of participants enrolled through four prisons in New South Wales, Australia. Two prisons (Goulburn, and Lithgow) predominantly house people in maximum-security prisons (male prisons), and two prisons predominantly house people in medium-security prisons, one male (Outer Metropolitan Multi-Purpose Correctional Centre; OMMPCC), and one female (Dillwynia) prison. These prisons had a combined cross-sectional population of 1,452 incarcerated individuals in 2016 (Appendix p1).[11] of whom approximately one third were unsentenced (i.e., on remand). All prisons offered harm reduction services, including opioid agonist therapy (OAT), access to the quaternary ammonium disinfectant, Fincol (Jasol, North Ryde, NSW, Australia) to cleanse injecting equipment, but not needle-syringe programs. Participant enrolment started in October 2014 at Goulburn, in July 2015 at Lithgow, and in April 2016 at OMMPCC, and Dillwynia.

The SToP-C study consisted of two major phases: a pre-DAA treatment scale-up phase or surveillance phase), and DAA treatment scale-up phase. In the initial phase of the study (pre-DAA treatment scale-up) from October 2014 to mid-2017, HCV treatment was standard of care through a nurse-led model of care,[12,13] including interferon-based treatment until March 2016 when DAA treatment became available following the Australian Government subsidised listing,[14] which included access for those in custody.[13] Standard of care HCV treatment numbers remained relatively low throughout this phase. In the second phase of the study, rapid scale-up of DAA treatment started from mid-2017 (June 2017 in Goulburn and Lithgow; September 2017 in Dillwynia; and October 2017 in OMMPCC), and ran until study closure in November 2019. The SToP-C study was therefore designed to evaluate the DAA treatment scale-up (provided by

SToP-C as a trial intervention), compared to interferon therapy as standard of care but with an expectation that DAAs would become the standard within the duration of the trial. We hypothesized low treatment uptake in the initial phase of the study, even with DAA as standard of care, given the limited capacity of prison health services.

Study participants

All prison inmates who were at least 18 years old were eligible for enrolment, irrespective of HCV infection status, HCV treatment history, risk behaviours, or sentence/remand status. Exclusion criteria were lack of adequate English to provide informed consent, and individuals with a security designation making clinic attendance for study visits logistically difficult. Participants who were transferred to a non-SToP-C prison, or released to freedom (i.e., returned to community) after enrolment, could re-enter the study if subsequently re-incarcerated into any SToP-C prison.

For the DAA intervention, participants with detectable HCV RNA underwent standard clinical and laboratory assessments. Participants with all HCV genotypes and liver disease stages (F0 to F4/compensated cirrhosis) were eligible for treatment. Exclusion criteria for treatment included clinical evidence of hepatic decompensation, ongoing severe psychiatric disease, or pregnancy. Laboratory exclusion criteria included alanine aminotransferase (ALT) and alanine aspartate (AST) levels >10 times upper limit of normal or platelet count <50,000/microlitre. People with current injecting drug use were eligible for treatment. Full eligibility criteria are provided in the study protocol, available at: https://kirby.unsw.edu.au/project/stop-c.

Study intervention and assessments

Following informed consent, participants were tested for HCV exposure and infection at enrolment (HCV antibody and RNA). Thus, from the enrolment visit, participants formed three sub-populations: 1) uninfected (HCV antibody negative); 2) previously infected (HCV antibody positive and HCV RNA negative); 3) infected (HCV antibody and HCV RNA positive). Uninfected and previously infected (i.e., HCV "at-risk") participants were followed for HCV primary infection and re-infection, respectively. Infected participants underwent pre-treatment clinical and laboratory assessments, transient fibro-elastography (FibroScan®), and evaluation of potential drug-drug interactions. During the initial phase, infected participants were referred for HCV treatment through the prison health service. During the second phase, from mid-2017 (rapid DAA treatment scale-up), participants eligible for HCV treatment were offered sofosbuvir/velpatasvir for 12 weeks, a pan-genotypic DAA regimen. Sofosbuvir/velpatasvir was administered orally once daily as a fixed-dose combination tablet (400 mg of sofosbuvir and 100 mg of velpatasvir). Participants who became re-infected post-treatment were offered re-treatment. All initial clinical assessments were conducted by specifically trained nurses, then the case was discussed with an infectious diseases specialist and treatment prescribed.[13]

Across the five-year study period, scheduled study visits were undertaken at enrolment, and then every three to six months. At enrolment, a demographic, clinical, and risk behavioural interview was administered by the research nurses. Risk behaviour questions included: injecting and non-injecting drug use type and frequency, sharing injecting equipment, non-drug use related HCV risks (e.g. tattooing, fights), receiving OAT, and using disinfectant to cleanse injecting equipment. The risk behaviour interview was repeated at all follow-up visits. At each visit, participants were also assessed for HCV infection or re-infection by HCV antibody and/or RNA testing. The study was promoted through awareness campaigns for correction officers, people incarcerated, and prison health care staff. Participants received a payment (AUD $10)

following each visit for participation. The value of this remuneration was approved by the ethics committees as an undue incentive (versus compensation for time and inconvenience) The study enrolment continued from October 2014 through to September 2019, with final follow-up in November 2019.

In the sub-population receiving treatment through SToP-C, additional study visits were undertaken at baseline (treatment initiation), week four of treatment, week 12 of treatment (end of treatment), and week 12 post-treatment. Assessments at these visits included symptom-directed physical examinations, assessment of HCV RNA, and standard laboratory testing. Study medication was dispensed four-weekly (for the majority) or on a daily observed basis, based on a standardised risk assessment for likely non-adherence. Participants transferred to a non-SToP-C prison continued DAA treatment, but not SToP-C study follow-up. Participants released to freedom were provided with their remaining therapy and a referral to a community primary care practitioner for follow-up.

Laboratory assessments

All samples were tested for HCV antibody and RNA in a central laboratory. The samples were tested for HCV Antibody using ARCHITECT Anti-HCV (Abbott, Chicago, IL, USA) and Murex anti-HCV (DiaSorin, Saluggia, Italy), for HCV RNA using COBAS TaqMan (Roche, Basel, Switzerland; lower limit of detection 15 IU/ml), hepatitis B surface antigen using ARCHITECT HBsAg (Abbott, Chicago, IL, USA), and HIV antibody using ARCHITECT HIV Ag/Ab Combo (Abbott, Chicago, IL, USA). HCV genotype was determined using COBAS HCV GT (Roche, Basel, Switzerland). Among participants with a positive HCV RNA test post-treatment, Sanger sequencing of the NS5A, NS5B, and Core-E2 regions of pre-treatment and

post-treatment samples was undertaken to determine if recurrent HCV viraemia was due to virological failure (homologous strains) or re-infection (heterologous strains).

Study definitions

Incident HCV primary infection was defined as a positive HCV antibody test among participants with a negative HCV antibody at the previous visit. Incident HCV re-infection was defined as a positive HCV RNA test among participants with a negative HCV RNA at the previous visit. Among participants receiving HCV treatment in the study, post-treatment re-infection was defined as a recurrent positive HCV RNA test after the end of treatment with an HCV strain that was confirmed as heterologous from the primary infecting strain.

Eligible for treatment was defined as participants with detected HCV RNA, no exclusion criteria for treatment, and at least one follow-up assessment after enrolment.

Among participants who received HCV treatment, an end-of-treatment response (ETR) was defined as non-quantifiable HCV RNA at end of treatment. HCV treatment outcome was classified as sustained virological response (SVR12, defined as non-quantifiable HCV RNA at or after 12 weeks following the end of treatment); virological failure (defined as quantifiable HCV RNA at 12 weeks after the end of treatment with re-infection excluded on sequencing); or non-virological failure (including re-infection, death, premature treatment discontinuation, or loss to follow up).

The date of incident HCV infection was estimated based on a hierarchical algorithm using serological, virological, and treatment data, as outlined below:

a. Participants with no HCV treatment following the previous visit: mid-point between last HCV negative and first HCV positive test (HCV antibody or HCV RNA).
b. Participants who received HCV treatment through SToP-C: mid-point between ETR and first HCV RNA positive test.
c. Participants who received HCV treatment outside of SToP-C (prison health service or community) and achieved SVR12: mid-point between documented SVR12 and first HCV RNA positive test.

Liver fibrosis stage was assessed by liver stiffness measurement (transient fibro-elastography). Significant liver fibrosis and cirrhosis were defined as liver stiffness >7.1 kPa and >12.5 kPa, respectively.[15] Compensated liver disease was defined by: an international normalized ratio (INR) <1.8, a serum albumin >30 gr/L, and a total serum bilirubin <35 micromol/L.

Study outcomes

The primary outcome was HCV incidence rate ratio, comparing before and after DAA treatment scale-up periods. Although DAA treatment scale-up commenced in mid-2017, it was staggered across the four prisons and high treatment coverage was not achieved until the end of 2017. Thus, the "after" DAA treatment scale-up period was designated as January 2018 onward. Changes in HCV incidence, including primary infection and re-infection were reported. The secondary study outcome was HCV treatment outcome.

Sample size calculation

The study sample size was calculated for 80% and 90% statistical power in different scenarios, assuming various levels of HCV incidence before treatment scale-up and expected incidence rate reduction after treatment scale-up (Appendix p1). Assuming a baseline HCV incidence of

10/100 person-years, the study needed 1,500, 310, and 106 person-years follow-up to have 90% power to detect 25%, 50%, and 75% incidence reduction, respectively.

Statistical analysis

The incidence of HCV infection (primary infection, re-infection and combined) and corresponding 95% confidence intervals (CI) was calculated as rates per 100 person-years using Poisson distribution, with follow-up censored at estimated date of incident HCV infection, last follow-up visit prior to prison transfer/release to freedom (where no return documented), or last study follow-up visit.

HCV incidence rates were calculated for periods before DAA treatment scale-up (2014 to 2017) and after DAA treatment scale-up (2018 to 2019). The rates between before and after treatment scale-up periods were compared by calculating the incidence rate ratio (IRR) and corresponding 95%CI, and by conducting a significance test (Mantel–Haenszel). HCV incidence rates were also calculated by six-monthly intervals across the whole study period. Given slower recruitment in the early stages of the study, the first interval was considered October 2014 to June 2016. Interrupted time series regression analysis,[16] was then used to evaluate change in trend in HCV incidence between periods before and after DAA treatment scale-up. The model was adjusted for calendar time (six-monthly interval) and HCV prevalence among new prison entrants, as a surrogate of the HCV reservoir transferring from community to prison over time. Prevalence of HCV infection among participants who were enrolled to the study within six months of entering the prison was used for this adjustment.

In stratified analysis, HCV incidence rates were compared between before and after treatment scale-up periods in three exclusive study population risk groups based on injecting drug use at

enrolment: i) participants who had never injected; ii) those who had a history of injecting but not in current imprisonment; iii) those who injected in current imprisonment.

The risk of HCV infection between before and after treatment scale-up periods was also assessed using unadjusted and adjusted Cox proportional hazard regression analyses, with *a priori* covariates including: gender, age, Australian Indigenous ethnicity, duration of stay in prison at enrolment, previous imprisonment, injecting drug use status at each visit, and prison site. Given that prison sites were gender specific (three men-only and one women-only prisons), gender was not included in the adjusted model due to collinearity with prison site. Injecting drug use status was included as a time-varying variable in the models. Other potential covariates (e.g., tattooing, having sex, and being in a fight in prison) were not included in the model, to maintain the focus of the analysis on major well-known HCV risk factors, particularly injecting drug use.

Given earlier commencement of participant enrolment in two maximum-security prison sites, a sensitivity analysis was performed restricting the analysis to participants from these two prisons. People in prison are highly transient, with many participants exiting the prison and re-entering during follow-up, in some of whom the estimated date of HCV incident infection fell during the time they were out of prison. Thus, another sensitivity analysis was performed excluding participants who were out of prison at their estimated date of HCV incident infection.

Statistical significances were assessed at $P<0.05$ (two-sided P values). Data analysis was performed using Stata 14.2 (StataCorp, College Station, TX, USA).

Study oversight

All participants provided written informed consent before study procedures. The study protocol was approved by New South Wales Justice Health and Forensic Mental Health Network Human Research Ethics Committee (HREC/14/JH/7), Aboriginal Health and Medical Research Council Human Research Ethics Committee (1047/14 and 1253/17) and New South Wales Corrective Services Ethics Committee. The study was conducted according to the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice (ICH/GCP) guidelines, and registered with clinicaltrials.gov (NCT02064049).

Role of the funding source

The study was funded jointly by the Australian National Health and Medical Research Council (NHMRC) and Gilead Sciences through a NMHRC Partnership Project grant. Gilead Sciences provided study medication. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The sponsor (The Kirby Institute, UNSW Sydney) collected the data, managed study samples, and monitored study conduct. The authors independently designed the study, supervised study conduct, had access to all data, performed the statistical analysis, drafted the manuscript, and had final responsibility for the decision to submit for publication.

RESULTS

Participant characteristics

A total of 3,691 participants were enrolled (30 October 2014 to 30 September 2019), representing a coverage of 53-89% of all people incarcerated in the four SToP-C prisons up to September 2019. Most participants were male (82%; n=3010/3691) with a median age of 33 years. Median duration of current imprisonment was nine months [inter-quartile range (IQR): 3, 29 months], while 28% (n=1029/3691) were on remand. More than half of participants (52%; n=1926/3691) reported a history of injecting drug use, while 31% (n=1134/3691) reported injecting drugs during current imprisonment, and 22% (n=797/3691) reported injecting in the past month in prison. Among participants who reported injecting drugs during the current imprisonment, 28% (n=315/1134) were currently receiving OAT at enrolment. Among those reporting injecting in the past month, 91% (n=722/797) reported sharing injecting equipment while in prison (Table 1).

At enrolment, among 3,691 participants, 2,240 (61%) had a negative HCV antibody (at-risk of primary HCV infection), 725 (20%) had a positive HCV antibody and negative HCV RNA (at-risk of HCV re-infection), and 719 (19%) had a positive HCV RNA (HCV infection; Figure 1). The prevalence of HCV infection at enrolment decreased from 29% among those enrolled before June 2016 to 10% among those enrolled after July 2019 (Figure 2A).

A total of 1,873 participants had at least one follow-up visit after enrolment. Baseline characteristics were comparable between participants with, and without, follow-up. As the only exception, those with follow-up had a longer time in prison at enrolment (median: 14 versus 6 months), and were less likely to be on remand (23% versus 33%; Appendix p2-3).

Clinical assessments and DAA treatment in participants with HCV infection

Among 719 participants HCV RNA positive at baseline, 315 (44%) had HCV genotype 1 infection, 308 (43%) genotype 3, and 26 (4%) other or mixed genotypes. In 70 participants, genotype results were not available (in n=67 due to low viral load). Twenty participants (3%) had severe liver fibrosis (F3) and 14 (2%) had cirrhosis (F4). No participant had HIV, while six (1%) had chronic hepatitis B.

A total of 499 HCV RNA positive participants had follow-up assessments after baseline, including 416 participants HCV RNA positive at baseline and 83 participants with incident HCV and no spontaneous clearance during follow-up. In the initial phase (October 2014 to mid-2017, pre-DAA treatment scale-up), 39 participants received HCV treatment though prison health service or in community during the time they returned to community (n=3 interferon-based therapy). In the second phase (mid-2017 to September 2019, post-DAA treatment scale-up), 349 participants received DAA treatment, among whom 324 participants received treatment through SToP-C and 25 participants through prison health service or in community (Figure 3).

Among 324 participants receiving treatment through SToP-C, 211 (65%) stayed in prison until end of treatment (completed treatment), while 113 participants (35%) exited before treatment completion due to prison transfer (n=63), release to freedom (n=48), or consent withdrawal (n=2). Among 143 participants who completed treatment and had an SVR12 assessment only two participants had virological failure (relapse).

HCV incidence

A total of 1,643 participants were at-risk of HCV during follow-up and contributed to the HCV incidence analysis (Figure 1). The at-risk population was 82% male (n=1350) with a median age of 33 years, and 31% (n=487) reported injecting drugs in the current imprisonment at enrolment (Appendix p2-3). Median follow-up was 10 months (IQR: 5, 18) in the overall analysis population, including 10 months (IQR: 5, 19) among participants sentenced and 8 months (IQR: 5, 14) among those on remand. Over 1,818 person-years of follow-up, 111 incident HCV infections were detected, including 57 primary infections and 54 re-infections. Five participants experienced two incident infection episodes (the second episode occurred following spontaneous or treatment-induce clearance of the first incident infection). The incidence rates of HCV infection, primary infection, and re-infection during the entire study follow-up were: 6.11/100 person-years (95% CI: 5.07, 7.35), 4.60/100 person-years (95%CI: 3.56, 5.96), and 9.34/100 person-years (95% CI: 7.15, 12.19), respectively. The HCV incidence was 5.48/100 person-years (95%CI: 4.40, 6.83) among sentenced participants and 9.07/100 person-years (95%CI: 6.34, 12.98) among those on remand.

HCV incidence increased prior to treatment scale-up, from 6.73/100 person-years (95% CI: 3.91, 11.60) to 10.93/100 person-years (95% CI: 7.54, 15.82) through December 2017. Following HCV treatment scale-up, the incidence declined to 5.13/100 person-years (95% CI: 3.10, 8.52) in January-June 2018, and was between 2.20 and 5.60/100 person-years for the remainder of the study (Figure 4).

The analysis comparing the incidence rate before treatment scale-up (2014-17) with after treatment scale-up (2018-19), indicated a 48% reduction from 8.31 to 4.35/100 person-years (IRR: 0.52, 95%CI: 0.36, 0.78, P<0.01). The HCV incidence reduction was 57% for primary

infection (from 6.64 to 2.85/100 person-years; IRR: 0.43, 95%CI: 0.25, 0.74, P<0.01) and 41% for re-infection (from 12.36 to 7.27/100 person-years; IRR: 0.59, 95%CI: 0.35, 1.00, P=0.05; Table 2).

The prevalence of HCV infection among participants enrolled within six months of entering the prison decreased from 27% (n=36/135) among those enrolled before June 2016, to 12% (n=15/125) among those enrolled after July 2019 (Figure 2B), suggesting reductions in HCV reservoir transferring from community to prison during the study period. The interrupted time series regression analysis adjusted for calendar time (underlying trend) and HCV prevalence among new prison entrants, the change in trend of HCV incidence following DAA treatment scale-up was still significant (adjusted IRR: 0.43, 95%CI: 0.21, 0.88, P=0.02). This analysis also indicated reductions in HCV primary infection (adjusted IRR: 0.41, 95%CI: 0.15, 1.11, P=0.08), and HCV re-infection (adjusted IRR: 0.44, 95%CI: 0.16, 1.20, P=0.11), although neither was statistically significant.

In the stratified analysis by injecting drug use status at enrolment, participants who reported a history of injecting but not in current imprisonment, had a 60% reduction in HCV incidence from 10.30 to 4.10/100 person-years (IRR: 0.40, 95%CI: 0.16, 0.98, P=0.04). Among participants who reported injecting in current imprisonment, HCV incidence reduction was 53%, from 21.74 to 10.25/100 person-years (IRR: 0.47, 95%CI: 0.30, 0.75, P<0.01). HCV incidence among participants who reported never injecting drugs was low throughout the study (Table 2).

The Cox proportional hazard regression analysis indicated a 50% reduction in the risk of HCV infection during 2018-19 compared to 2014-17 after adjustment for participants' age,

Indigenous Australian ethnicity, duration of stay in the prison, previous imprisonment, injecting drug use status, and prison site [adjusted Hazard Ratio (HR): 0.50 (95% CI: 0.33, 0.76, P<0.01); Table 3]. Independent of study period, risk of HCV infection was lower in older participants (adjusted HR for each year increase in age: 0.92, 95% CI: 0.89, 0.95, P<0.01), and higher among participants with previous imprisonments (adjusted HR: 2.27, 95% CI: 1.21, 4.26, P=0.01). Compared to participants reporting no injecting in current imprisonment, risk of HCV infection was three-time higher among those who injected longer than six months ago (adjusted HR: 3.32, 95% CI: 1.04, 10.59, P=0.04), and six times higher among those who injected during the previous six months (adjusted HR: 6.14, 95% CI: 3.16, 11.92, P<0.01; Table 3).

In a sensitivity analysis, restricting the study population to participants enrolled from two maximum-security prisons, results were similar (Appendix p4,6). In another sensitivity analysis, participants whose estimated date of HCV incident infection fell in the time when they were out of prison were excluded (n=33), but the results were similar (Appendix p5).

DISCUSSION

The SToP-C study provides empirical evidence for HCV treatment-as-prevention in the prison setting, with a significant reduction in HCV incidence following rapid scale-up of DAA therapy in four prisons in New South Wales, Australia. The findings support enhanced HCV treatment access and coverage among incarcerated people, including unrestricted access to DAA treatment and rapid treatment scale-up, to improve individual health outcomes and boost HCV elimination efforts within the prison and broader community settings.

The observed incidence of HCV infection prior to DAA treatment scale-up was 8.3/100 person-years, consistent with a previous study from New South Wales prisons which only included people who inject drugs and documented an HCV incidence of 11.4/100 person-years.[17] Of note, HIV prevalence in Australian prisons is very low,[18] (zero in our study), contrasting with many other prison settings.[19]

A reduction in HCV incidence from 8.3 to 4.4/100 person-years following DAA treatment scale-up was demonstrated in the SToP-C study. Although a decrease in HCV prevalence among new prison entrants was also observed during the study period, the analysis adjusted for HCV prevalence, still showed a significant reduction in HCV incidence, providing strong evidence of HCV treatment-as-prevention, particularly in a setting where harm reduction measures may not be optimal.

As expected, the HCV incidence was higher among participants with a prior history of injecting drug use, and was highest among those reporting injecting within the past month. Further, the greatest reduction in HCV incidence following DAA treatment scale-up was among the people who injected drugs, including reducing HCV risk by more than half among the highest risk

population with recent injecting drug use. HCV incidence was consistently very low among the 45% of the SToP-C study population without a history of injecting drug use at enrolment. This finding also suggests good validity of the self-reported HCV risk behaviour, and a low risk of HCV transmission through non-injecting means.

There are several reasons for the non-significant impact of DAA treatment scale-up on HCV re-infection. First, statistical power was more limited than for the overall HCV incidence evaluation or for primary infection. Second, detection of HCV re-infection is partly related to frequency of HCV RNA testing.[20,21] Primary infection is determined on the basis of HCV antibody seroconversion which is sustained. In contrast, re-infection cases can undergo spontaneous clearance and avoid detection, particularly in a setting of six-monthly HCV RNA testing.[22] Finally, HCV treatment of high-risk individuals initially expands the susceptible population for HCV re-infection and thereby increases the risk level in this population. Irrespective of these potential explanations, further strategies are required to reduce HCV re-infection in the prison setting, e.g., enhanced harm reduction interventions.

During the first two years of access to prison health service-led DAA treatment (2016-17), only 45 participants received treatment, whereas in the first six months after scale-up via SToP-C, 142 participants received treatment, highlighting the feasibility of rapid scale-up. The rapid transition from diagnosis to treatment initiation is likely to boost treatment-as-prevention effect by reducing loss to follow-up and limiting the chance of ongoing transmissions. In the SToP-C study, the care cascade was used with venepuncture sampling and HCV testing in a central laboratory, necessitating several weeks delay in treatment initiation. By contrast, point-of-care HCV testing in prison has been shown to result in a significantly shorter time to treatment and increased treatment uptake.[23,24]

Only a minority of the SToP-C participants (28%) were receiving OAT. A previous analysis of risk behaviours in a prospective cohort of people in Australian prisons who inject drugs, revealed increased risk behaviour following incarceration, with increased rates of sharing injecting equipment and increased use of opioids, including heroin and diverted methadone or buprenorphine.[25] Mathematical modelling of HCV transmissions in the New South Wales prisons has demonstrated that DAA treatment scale-up to 40% of all people in prisons with HCV infection provided an effect size on incidence reduction comparable to that reported in the SToP-C study.[5] Further, the modelling revealed that the combination of DAA treatment scale-up with enhanced access to OAT enabled greater HCV incidence reduction. Accordingly, expansion of OAT, including access to depot-buprenorphine preparations, in the prison setting should further reduce HCV risk behaviour. Although there are clear barriers to implementation,[26] consideration needs to be given to evaluation of prison-based needle and syringe programs to match broad Australian community-based access. Continued HCV elimination efforts, particularly among community-based people who inject drugs, should also reduce HCV prevalence among people entering prison as was observed over time amongst those newly incarcerated who enrolled in the SToP-C study.

Interferon-based treatment, was previously a major barrier against treatment uptake, given the significant side effects and long treatment duration. By contrast, DAA treatment has shifted the paradigm of HCV therapy with once daily oral dosing, minimal side effects, short duration, and very high efficacy. However, HCV treatment programs in prison settings worldwide have been relatively limited, often with small numbers of HCV infected individuals being treated.[27,28] In Australia, specific arrangements were put in place to ensure prison-based access to the DAA treatment program which has led to a steady increase in treatment uptake in Australian

correctional centres. While prison-based DAA treatment initiations constituted approximately 6% of the national DAA treatment uptake in 2016,[29] this figure increased to 31% in 2019,[30] crucial for national elimination efforts. DAA treatment scale-up in prison is also important for elimination efforts outside prison, given high transitioning between prison and community. We could not assess the impact of HCV treatment scale-up in prison on HCV transmission in the community given it was out of the scope of this study. Incarceration, however, if often a missed opportunity to provide HCV care to a highly marginalised population.[31] An HCV testing and treatment program in Italian prisons reported that 81% of people diagnosed with HCV through screening in prison never received HCV care before incarceration.[32] Surveillance of DAA treatment uptake in prison settings, therefore, is a key element of national elimination efforts.

Once the SToP-C DAA treatment scale-up commenced, the uptake of DAA therapy among those with HCV was encouraging, with most individuals who were available for post-screening follow-up initiating therapy. The reasons for non-initiation of treatment were primarily related to the dynamic population of people in prison, including frequent transfers to other prisons and release to freedom. High DAA uptake was seen, despite earlier qualitative research from the SToP-C prior to DAA scale-up identifying concerns around HCV re-infection as a potential barrier to treatment initiation.[33] Further studies are required to evaluate interventions to maintain the continuum of care for people diagnosed with HCV in prison, but transitioning, including initiatives for referral to community services for those released to freedom or to other prison health services for those transferred.

The limitations of the SToP-C study firstly include a before and after evaluation design, rather than a larger cluster randomised controlled trial conducted across the 40 New South Wales prisons. However, adequate resources for such a large undertaking were not available.

Secondly, although enrolment coverage (i.e., the proportion of all those incarcerated in the four study prisons who were enrolled in the SToP-C study) reached over 80%, risk status and transmissions through people not enrolled in the study were not able to be measured. Third, the rate of transitioning of enrolled individuals between prisons, and of release to freedom was higher than anticipated, even among those incarcerated in maximum-security prisons. It is apparent that the often-used term "a captive population" to describe incarcerated people in the context of HCV elimination efforts is inappropriate both in terms of stigma and epidemiological reality. Less than half of participants had no follow-up visit, and among those with follow-up only 41% had follow-up extending beyond 12 months, demonstrating the highly dynamic nature of the population. However, background and behavioural characteristics of participants with and without follow-up were comparable, suggesting minimal chance of selection bias. Finally, although the study included one female prison, this centre had the lowest relative enrolment and person-years follow-up, making a stratified analysis by gender problematic.

In conclusion, the SToP-C study has demonstrated an HCV treatment-as-prevention effect associated with DAA treatment scale-up in the prison setting. The findings support enhanced DAA therapy delivery for incarcerated populations, while suggest further consideration of HCV treatment-as-prevention strategies among the broader population at risk of HCV infection. The combination of rapid DAA scale-up with efficient HCV diagnosis, and enhanced primary HCV prevention strategies are likely to provide even greater impacts on HCV transmission given the high transmission risk associated with injecting drug use in the prison setting.

CONTRIBUTORS

GJD and ARL designed and proposed the study, with contributions in study design and drafting the grant from JG, TB, NKM, GMC, CT, JGMc, DMB, and JA. GJD, BH, JG, MB, PM, and ARL were involved in study coordination and supervision. GJD, JG, TB, CT, PV, NKM, GMC, LG, CM, and ARL provided study governance through the Protocol Steering Committee. BH conducted the data analyses, with assistance from EBC and HM and with oversight from JA and GJD. BH, ARL and GJD verified the data, and drafted the manuscript, with input from all authors. All authors have seen and approved the final version of the manuscript.

DECLARATION OF INTERESTS

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DATA SHARING STATEMENT

Individual participant data that underlie the results reported in this article and a data dictionary will be available, after de-identification (text, tables, figures, and appendices), beginning 9 months and ending 36 months following article publication. Data requests, including a methodologically sound proposal, may be submitted to the Kirby Institute (recpt@kirby.unsw.edu.au). The Study Steering Committee will review the data request applications. Following approval, the data will be shared to achieve aims in the approved

proposal. The data requestors will need to sign a data access agreement before having access to the data. The study protocol is publicly available at: https://kirby.unsw.edu.au/project/stop-c

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TABLES

Table 1: Background and behavioural characteristics of SToP-C study participants at enrolment, overall and by year of enrolment

	Total (n=3691)	Year of enrolment				
		2014-15 (n=376)	2016 (n=703)	2017 (n=901)	2018 (n=1009)	2019 (n=702)
Prison site, n (%)						
Goulburn	1,162 (31)	304 (81)	188 (27)	270 (30)	268 (27)	132 (19)
Lithgow	957 (26)	72 (19)	241 (34)	289 (32)	218 (22)	137 (20)
OMMPCC	891 (24)	0	161 (23)	210 (23)	308 (31)	212 (30)
Dillwynia	681 (18)	0	113 (16)	132 (15)	215 (21)	221 (31)
Gender, n (%)						
Female	679 (18)	0	113 (16)	132 (15)	215 (21)	219 (31)
Male	3010 (82)	376 (100)	590 (84)	769 (85)	794 (79)	481 (69)
Transgender	2 (<1)	0	0	0	0	2 (<1)
Age (year), median (IQR)	33 (26, 41)	34 (26, 44)	34 (27, 41)	32 (26, 39)	33 (27, 40)	32 (26, 40)
Aboriginal and or Torres Strait Islander, n (%)						
No	2563 (69)	275 (73)	477 (68)	631 (70)	728 (72)	452 (64)
Yes	1005 (27)	95 (25)	174 (25)	236 (26)	279 (28)	221 (31)
Not available	123 (3)	6 (2)	52 (7)	34 (4)	2 (<1)	29 (4)
Country of birth, n (%)						
Australia	2905 (79)	309 (82)	530 (75)	703 (78)	802 (79)	561 (80)
Other countries	668 (18)	62 (16)	123 (18)	164 (18)	206 (20)	113 (16)
Not available	118 (3)	5 (1)	50 (7)	34 (4)	1 (<1)	28 (4)
Formal education level, n (%)						
No formal education or completed primary school	1238 (34)	127 (34)	244 (35)	335 (37)	285 (28)	247 (35)
Completed high school	1709 (46)	162 (43)	312 (44)	430 (48)	517 (51)	288 (41)
Tertiary education	613 (17)	80 (21)	97 (14)	98 (11)	203 (20)	135 (19)
Not available	131 (4)	7 (2)	50 (7)	38 (4)	4 (<1)	32 (5)
Duration of stay in current prison (month), median (IQR)	9 (3, 29)	29 (10, 58)	13 (5, 36)	9 (3, 29)	7 (2, 23)	5 (2, 17)
Previous imprisonment, n (%)						
No	967 (26)	112 (30)	171 (24)	224 (25)	291 (29)	169 (26)
Yes	2607 (71)	259 (69)	482 (69)	643 (71)	718 (71)	505 (71)
Not available	117 (3)	5 (1)	50 (7)	34 (4)	0	28 (4)
Tattoo or piercing in the prison (current imprisonment)						
No	3152 (85)	343 (91)	567 (81)	758 (84)	879 (87)	605 (86)
Yes	419 (11)	30 (8)	77 (11)	103 (11)	130 (13)	79 (11)
Not available	120 (3)	3 (1)	59 (8)	40 (4)	0	120 (3)

	Total (n=3691)	Year of enrolment				
		2014-15 (n=376)	2016 (n=703)	2017 (n=901)	2018 (n=1009)	2019 (n=702)
Injecting drug use status, n (%)						
Never injected	1654 (45)	170 (45)	271 (39)	395 (44)	496 (49)	322 (46)
Had history of injecting, but not in current imprisonment	792 (21)	63 (17)	126 (18)	206 (23)	229 (23)	168 (24)
Injected longer than 6 months ago (current imprisonment)	139 (4)	39 (10)	37 (5)	22 (2)	19 (2)	22 (3)
Injected in the previous 2-6 months (current imprisonment)	198 (5)	24 (6)	48 (7)	51 (6)	48 (5)	27 (4)
Injected in the previous month (current imprisonment)	797 (22)	76 (20)	176 (25)	191 (21)	217 (22)	137 (20)
Not available	111 (3)	4 (1)	45 (6)	36 (4)	0	26 (4)
Opioid agonist therapy*, n (%)						
Never	591 (52)	46 (33)	114 (43)	143 (53)	177 (62)	111 (60)
Yes, previously	237 (21)	34 (24)	80 (30)	81 (30)	72 (25)	48 (26)
Yes, currently	315 (28)	59 (42)	71 (27)	45 (17)	35 (12)	27 (15)
Frequency of injecting†, n (%)						
Less frequently than once a week	189 (24)	23 (30)	46 (26)	50 (26)	44 (20)	26 (19)
1 to 6 days per week, not daily	209 (26)	17 (22)	54 (31)	43 (23)	57 (26)	38 (28)
Once a day or more	389 (49)	36 (47)	72 (41)	92 (48)	116 (53)	73 (53)
Not available	10 (1)	0	4 (2)	6 (3)	0	0
Re-used a needle or syringe after someone else had used it†, n (%)						
No	76 (10)	12 (16)	13 (7)	16 (8)	22 (10)	13 (10)
Yes	709 (89)	63 (83)	159 (90)	168 (88)	195 (90)	124 (91)
Not available	12 (2)	1 (1)	4 (2)	7 (4)	0	0
Re-used any injecting equipment after someone else had used it†, n (%)						
No	63 (8)	9 (12)	13 (7)	14 (7)	19 (9)	8 (6)
Yes	722 (91)	66 (87)	159 (90)	170 (89)	198 (91)	129 (94)
Not available	12 (2)	1 (1)	4 (2)	7 (4)	0	0

* Among participants who injected anytime in current imprisonment (n=1134)

† Among participants who injected in the previous month in current imprisonment (n=797)

Table 2: Comparison of the incidence rates of HCV infection between before and after 2017, in overall and by injecting drug use status at enrolment

	Person-years follow-up	Incident n	Incidence rate (95% CI), per 100 person-years	Incidence Rate Ratio (95% CI)	P value
HCV primary and re-infection					
Total participants					
2014-17	807	67	8.31 (6.54, 10.55)	1.00	
2018-19	1,011	44	4.35 (3.24, 5.85)	0.52 (0.36, 0.78)	<0.01
Participants never injected					
2014-17	458	7	1.53 (0.73, 3.20)	1.00	
2018-19	541	7	1.29 (0.62, 2.72)	0.84 (0.30, 2.42)	0.76
Participants with a history of injecting, but not in current imprisonment					
2014-17	126	13	10.30 (5.98, 17.73)	1.00	
2018-19	171	7	4.10 (1.95, 8.60)	0.40 (0.16, 0.98)	0.04
Participants who injected in current imprisonment					
2014-17	216	47	21.74 (16.34, 28.94)	1.00	
2018-19	293	30	10.25 (7.17, 14.67)	0.47 (0.30, 0.75)	<0.01
HCV primary infection					
Total participants					
2014-17	572	38	6.64 (4.83, 9.13)	1.00	
2018-19	667	19	2.85 (1.82, 4.46)	0.43 (0.25, 0.74)	<0.01
Participants never injected					
2014-17	447	5	1.12 (0.47, 2.69)	1.00	
2018-19	524	7	1.34 (0.64, 2.80)	1.19 (0.38, 3.76)	0.76
Participants with a history of injecting, but not in current imprisonment					
2014-17	61	10	16.34 (8.79, 30.38)	1.00	
2018-19	80	4	5.00 (1.88, 13.32)	0.31 (0.10, 0.98)	0.03
Participants who injected in current imprisonment					
2014-17	59	23	39.08 (25.97, 58.82)	1.00	
2018-19	57	8	14.03 (7.02, 28.5)	0.36 (0.16, 0.80)	<0.01
HCV re-infection					
Total participants					
2014-17	235	29	12.36 (8.59, 17.79)	1.00	
2018-19	344	25	7.27 (4.92, 10.76)	0.59 (0.35, 1.00)	0.05
Participants never injected					
2014-17	12	2	17.02 (4.26, 68.07)		
2018-19	17	0	0.00 (0.00, 17.65)*	-	-
Participants with a history of injecting, but not in current imprisonment					
2014-17	65	3	4.61 (1.49, 14.30)	1.00	
2018-19	91	3	3.31 (1.07, 10.25)	0.72 (0.15, 3.55)	0.68
Participants who injected in current imprisonment					
2014-17	157	24	15.26 (10.23, 22.76)	1.00	
2018-19	236	22	9.34 (6.15, 14.19)	0.61 (0.34, 1.09)	0.09

* Given the zero event, 95%CI was calculated based on the "rule of 3".[34]

Table 3: Unadjusted and adjusted Cox Proportional Hazards models evaluating the factors associated with the risk of HCV infection

	Unadjusted Hazard Ratio (95% CI)	P value	Adjusted Hazard Ratio (95% CI)*	P value
Study period				
2014-17	1.00		1.00	
2018-19	0.55 (0.37, 0.82)	<0.01	0.50 (0.33, 0.76)	<0.01
Gender†				
Female	1.00			
Male	0.62 (0.39, 0.98)	0.04		
Age at enrolment (year)	0.92 (0.89, 0.94)	<0.01	0.92 (0.89, 0.95)	<0.01
Age at enrolment (year)				
25 years or younger	1.00			
25-35 years	0.67 (0.44, 1.01)	0.06		
35-45 years	0.30 (0.17, 0.53)	<0.01		
Older than 45 years	0.04 (0.01, 0.18)	<0.01		
Aboriginal and or Torres Strait Islander				
No	1.00		1.00	
Yes	2.01 (1.37, 2.96)	<0.01	1.02 (0.66, 1.57)	0.93
Duration of stay in current prison at enrolment				
Up to 12 months	1.00		1.00	
13-24 months	0.69 (0.40, 1.18)	0.17	0.92 (0.51, 1.67)	0.79
25-36 months	0.54 (0.28, 1.03)	0.06	0.89 (0.44, 1.82)	0.76
>36 months	0.39 (0.25, 0.63)	<0.01	0.82 (0.46, 1.44)	0.48
Previous imprisonment				
No	1.00		1.00	
Yes	3.02 (1.78, 5.14)	<0.01	2.27 (1.21, 4.26)	0.01
Injecting drug use status				
Not injected in current imprisonment	1.00		1.00	
Injected longer than 6 months ago (current imprisonment)	4.52 (1.61, 12.73)	<0.01	3.32 (1.04, 10.59)	0.04
Injected in the previous 6 months (current imprisonment)	10.32 (5.27, 20.20)	<0.01	6.14 (3.16, 11.92)	<0.01
Prison site at the last visit†				
Lithgow	1.00		1.00	
Dillwynia	2.05 (1.16, 3.62)	0.01	2.10 (1.06, 4.15)	0.03
Goulburn	2.02 (1.26, 3.25)	<0.01	1.97 (1.18, 3.29)	<0.01
OMMPCC	0.53 (0.25, 1.14)	0.10	1.18 (0.53, 2.63)	0.69

* 1,785 person-year follow-up with 110 incident events included in the model

† Gender was not included in the adjusted model given high collinearity with prison site

FIGURES

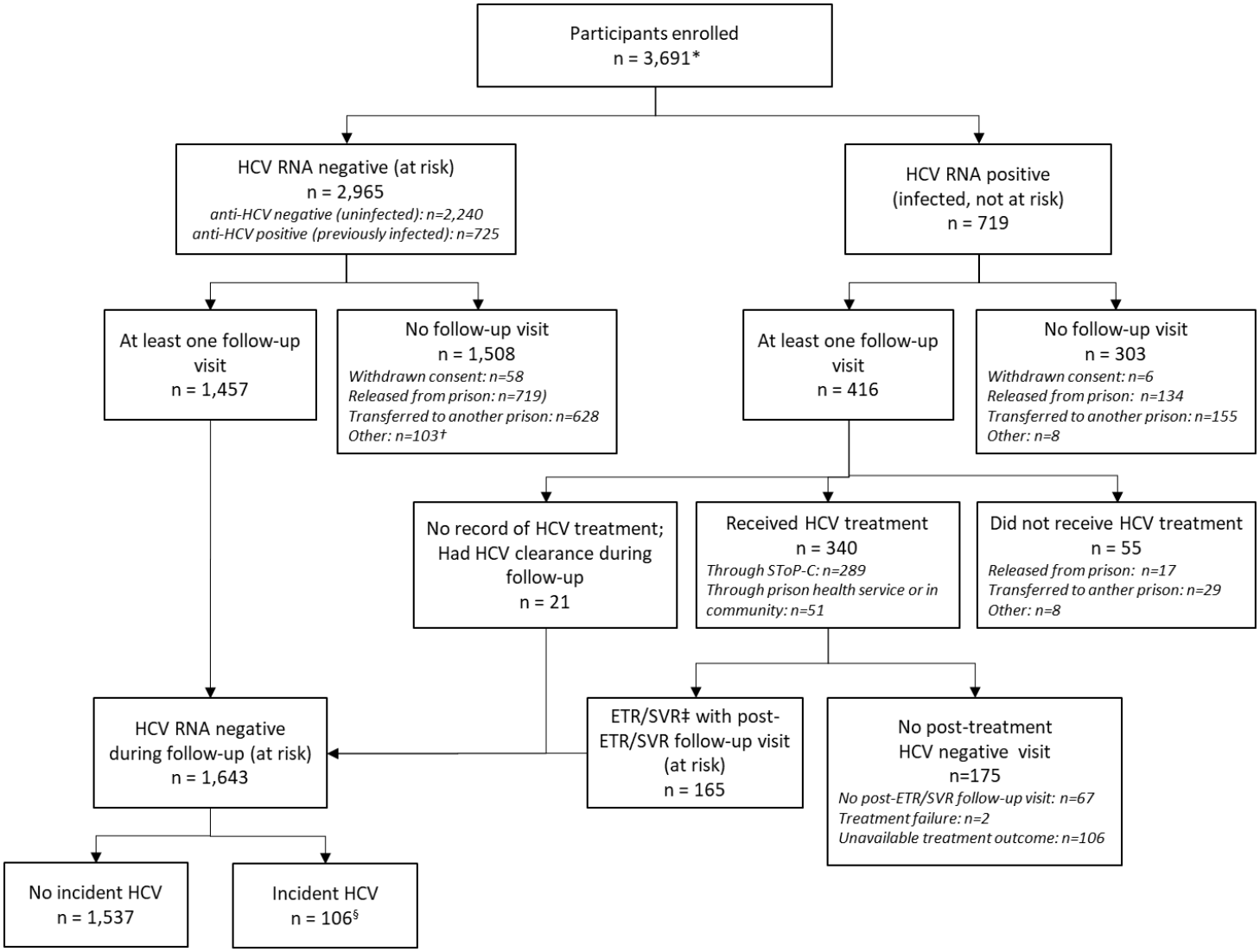


Figure 1: Overview of SToP-C study participants

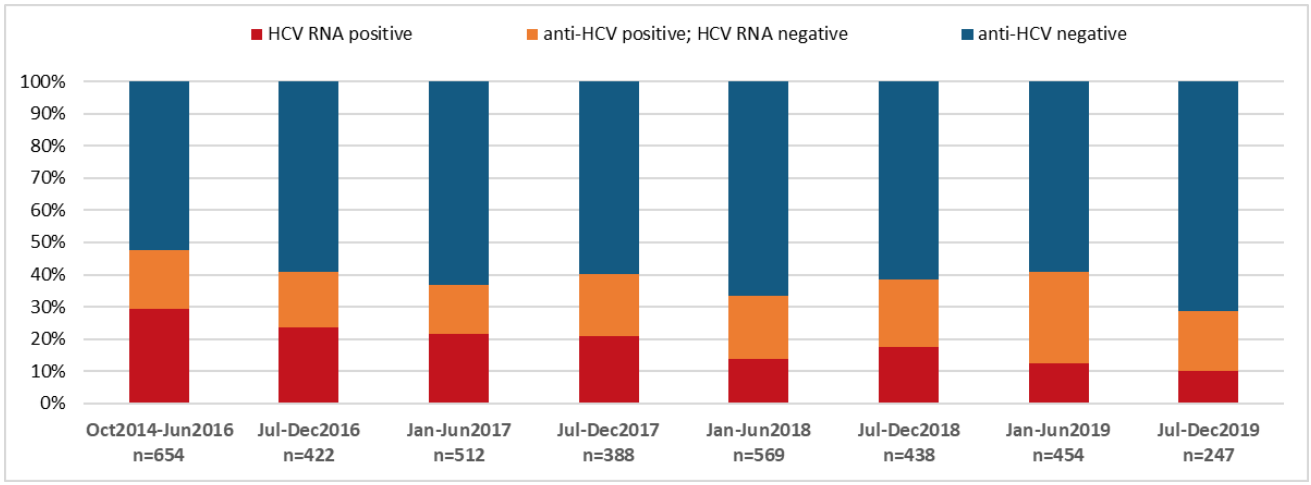
* HCV test results at enrolment were not available for 7 participants.

† Most (n=96) are participants who were enrolled during late 2019 and were not due for follow-up or there was no access to the participant by the end of the study.

‡ For participants receiving treatment through SToP-C, ETR was considered given that phylogenetic analysis was used to distinguish post-treatment re-infection from relapse. For other participants SVR was considered.

§ Five participants experienced the second incident HCV infection after clearance (total HCV incident events=111).

A.



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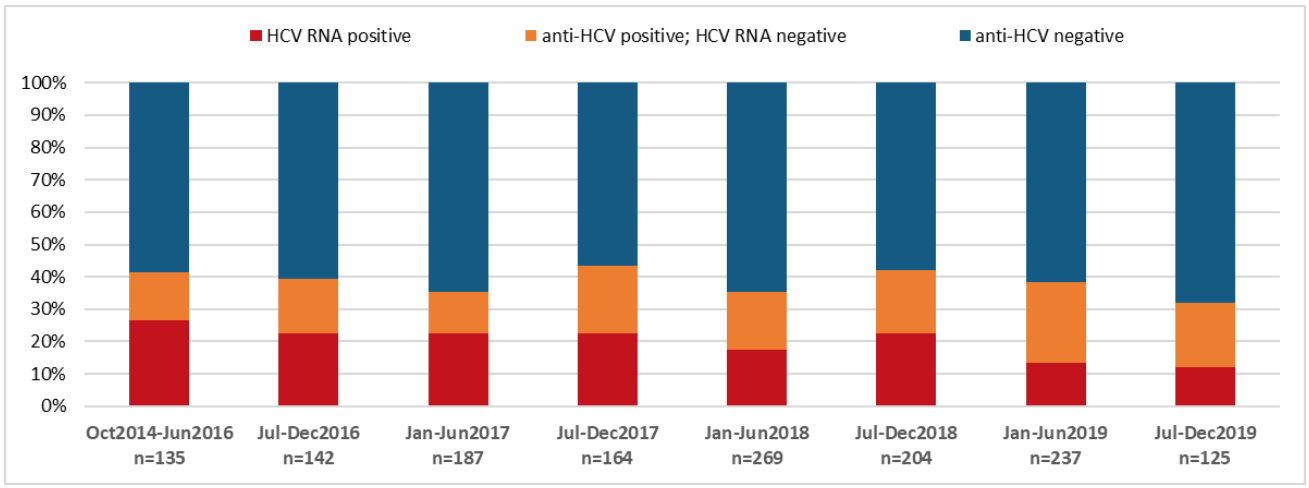


C.

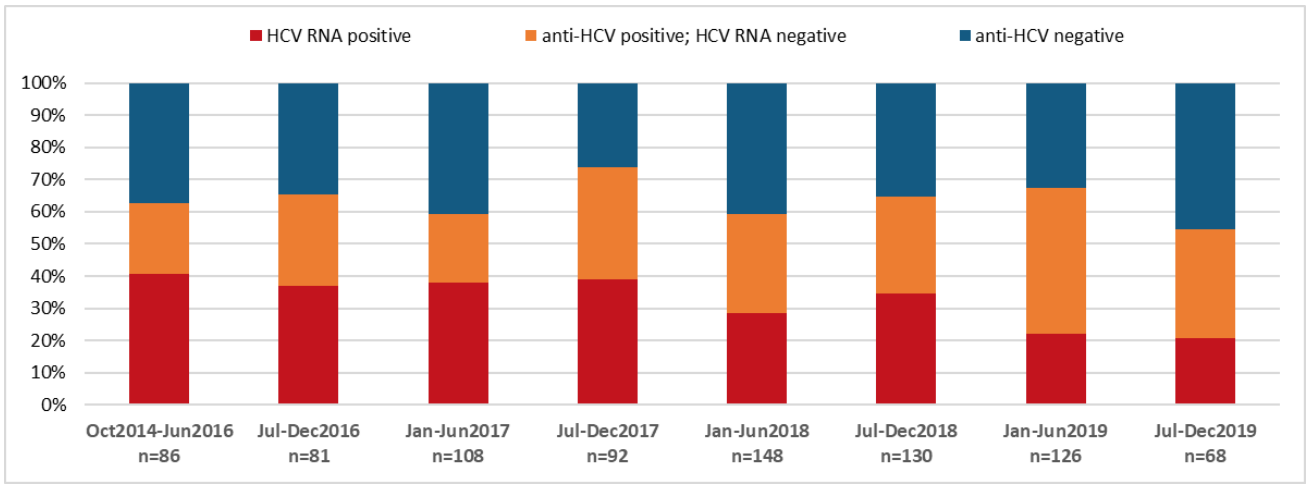


Figure 2: HCV status at enrolment by year of enrolment among total SToP-C participants (A), among total new prison entrants (B), and among new prison entrants who have ever injected drugs at enrolment (C)

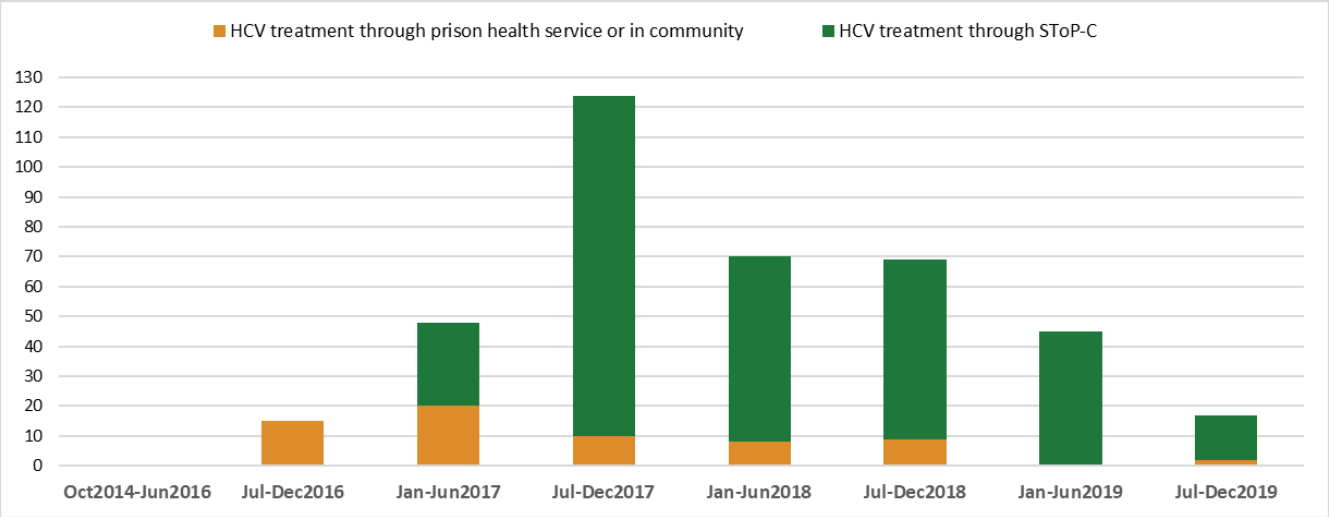
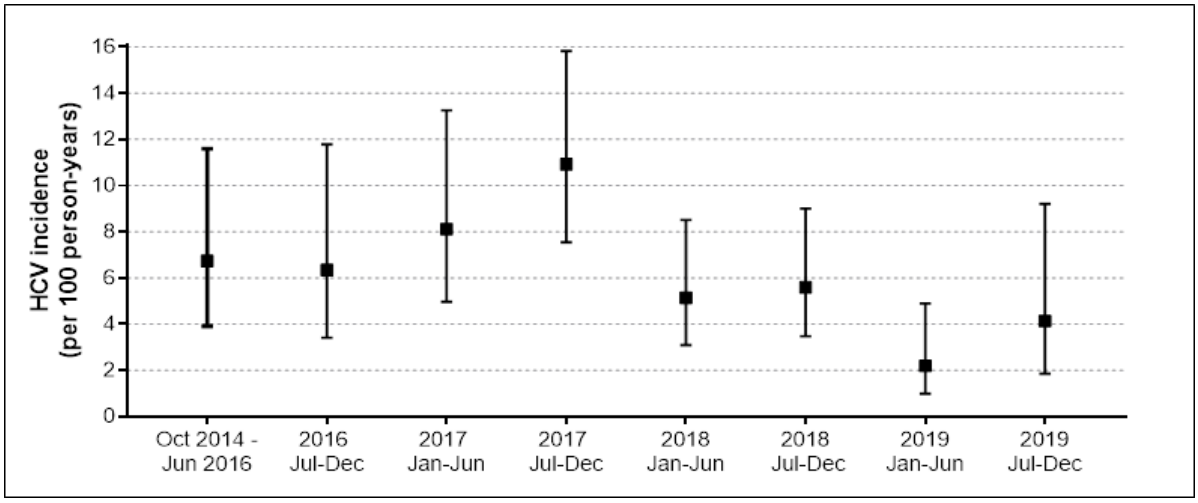
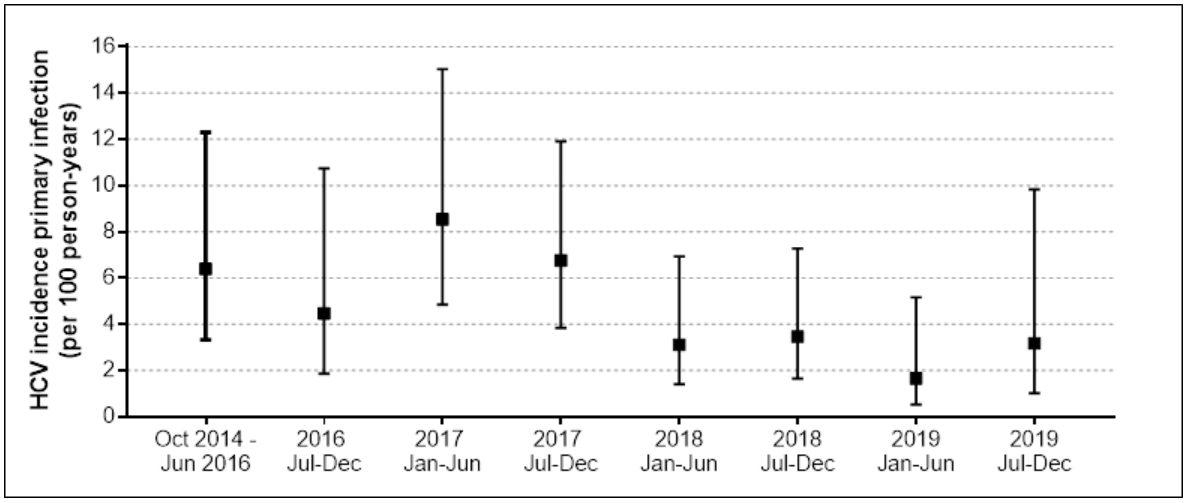


Figure 3: Number of participants receiving HCV treatment through the SToP-C study or outside of the study, by year of enrolment

A.



B.



C.

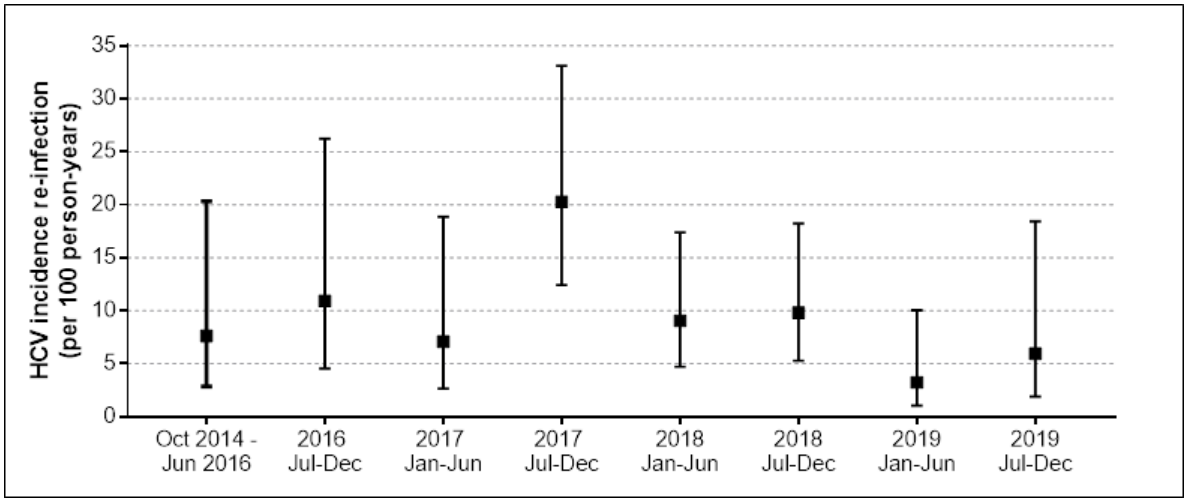
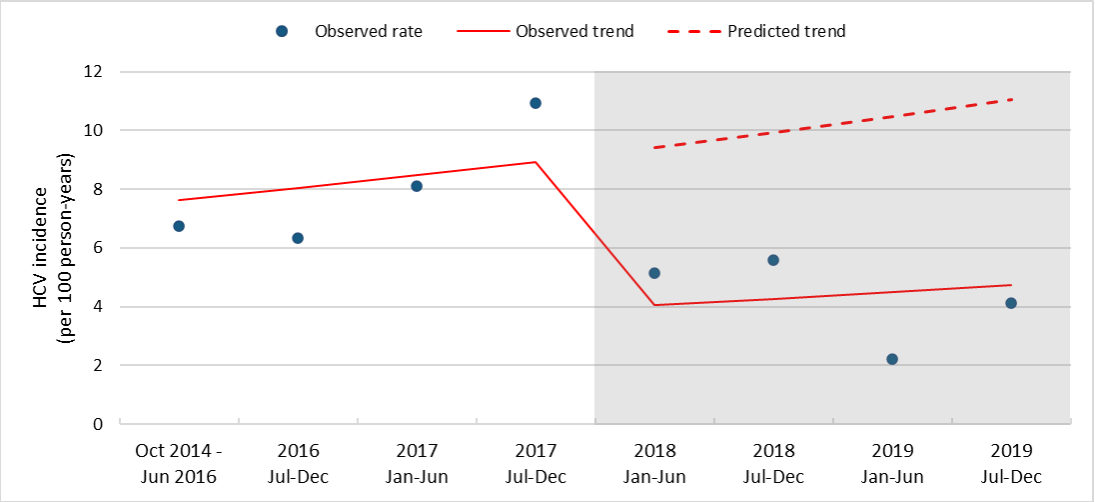


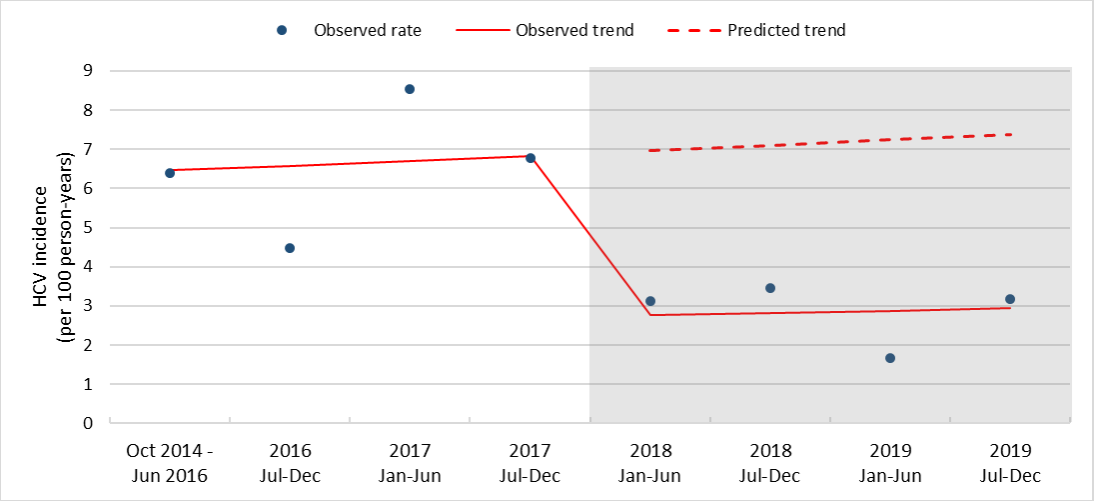
Figure 4: Biannual incidence of all HCV infection (A), primary HCV infection (B), and HCV re-infection (C) in the SToP-C study

The time period between October 2014 and June 2016 was merged to increase person-years follow-up

A.



B.



C.

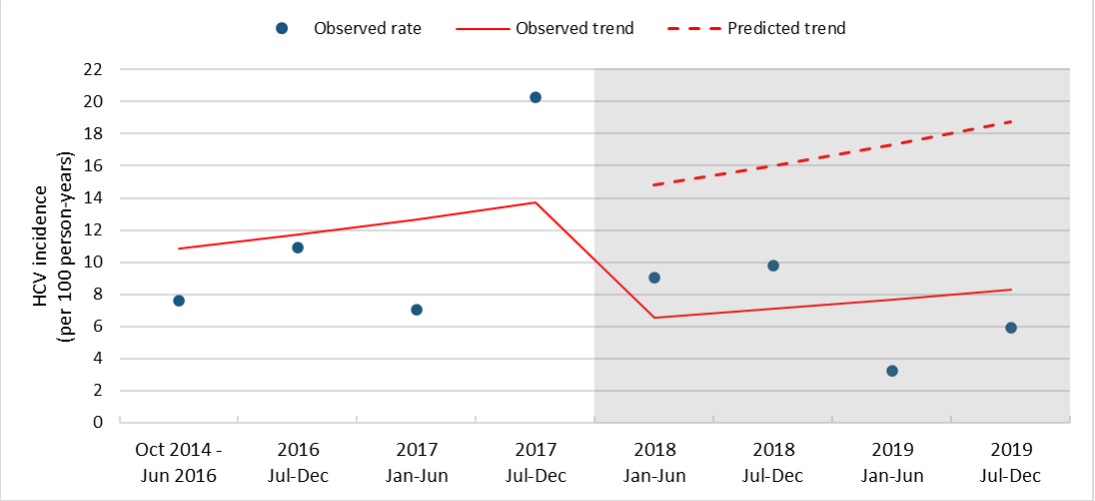


Figure 5: The trend of incidence of all HCV infection (A), primary HCV infection (B), and HCV re-infection (C) in the SToP-C study

Red solid line represents the observed trend and red dashed line represents predicted counterfactual by removing the effect of the intervention for after 2017